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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,208	ZAMORA, PAUL O.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *29-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election with the Group II, claims 1-28, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 29-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Claim Objections

2. For clarification purpose, suggest rewording of "comprises" to "is" in claims 5, 6, 7, 10-12, 18 and 19. For instance "the multifunctional crosslinking agent comprises..." in claim 5 to "the multifunctional crosslinking agent is...".

For clarification purpose, suggest rewording of "the porous surface comprises expanded polytetrafluoroethylene" in 9 to "the porous surface is expanded polytetrafluoroethylene surface".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-28 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for a method of making a biocompatible medical

device by coating with the specific multifunctional cross-linking agent such as a bis-variant of polyethylene glycol, polyethylene oxide and polyethylene glycol" and the specific cross-linkable biomolecule, such as benzyl-bis(dimethylsilylmethyl)x-oxycarbamoyl-heparin or silyl-heparin, does not reasonably provide enablement for "a multifunctional crosslinking agent", "a cross-linkable biomolecule", "a cross-linkable adsorbable biomolecule" and/or "a cross-linkable adsorbable heparin activity biomolecule". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The specification defines "multifunctional crosslinking agent" as "a multifunctional compound with at least two functional groups, constituting a bifunctional crosslinking agent if two functional groups are present; "cross-linkable biomolecule" as "cross-linkable biologically active molecule"; "heparin activity biomolecule" as "a

biomolecule which includes heparin or derivative and related molecules" (page 15, lines 13-14; page 16, lines 16-17; page 17, line 5-6).

The interpretation of the instant claims allows for the inclusion of plethora agents having the desired characteristics that are known today, for example (i) multifunctional crosslinking agent such as polyethylene glycol crosslinking agents, polyethylene oxide crosslinking agents, acrylic crosslinking agents, methacrylic crosslinking agents, cyanurate crosslinking agents, isocyanurate crosslinking agents, aziridinyl crosslinking agents, polycarbodiimide crosslinking agents, etc... and (ii) cross-linkable biomolecule such as collagen, gelatin, elastin, fibronectin, glycosaminoglycans, antibacterial, enzyme, dyes, nucleic acids, antibodies, antigens, drugs, vitamins, anticoagulant and etc..., and those that may be discovered in the future.

The specification discloses a medical device, particularly vascular graft, composed of expanded polytetrafluoroethylene where polyethylene glycol, such as bis-benzotriazole carbonate polyethylene glycol, dissolved in organic solvent is coated on the said medical device, followed by coating of silyl-heparin dissolved in second solvent, such as benzyl-bis(dimethylsilylmethyl)x-oxycarbamoyl-heparin and a method of making said medical device, as the specific embodiment of the invention (Examples).

It is generally recognized in the art that biological compounds often react unpredictably under different circumstances (Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)). For instance, the activity of multifunctional crosslinking agents are generally known to behave differently under different circumstances, depending upon their different binding

affinity to different active molecule and different chain length of atoms between two reactive groups (see USP 6596293; USP 4665164; USP 6294697).

The relative skill of the artisan and the unpredictability of the pharmaceutical art are very high. To practice the instant invention to the claimed scope, applicant would have to (i) screen potentially suitable agents and (iii) assay to find out which agents are able to behave similar to the exemplified BTC-PEG and cross-linked silyl-heparin and then (iv) extrapolate the test and result to the claimed utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the result provided in the instant specification to the larger and highly varied genera of agents that are characterized by "multifunctional crosslinking agent" and "cross-linkable biomolecule", "a cross-linkable adsorbable biomolecule" and "a cross-linkable adsorbable heparin activity biomolecule", without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural

compounds or even structurally related compounds, the limited number of working examples and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed "multifunctional crosslinking agent", "cross-linkable biomolecule", "a cross-linkable adsorbable biomolecule" and "a cross-linkable adsorbable heparin activity biomolecule" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently

claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-22 recite "a conjugate of at least one prosthetic hydrophobic unit and a heparin activity biomolecule" and "a conjugate of from 1 to 30 hydrophobic silyl moieties and the heparin activity biomoecule", respectively. The specification does not define the term(s) and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. In this regard, although "benzyl-bis(dimethylsilylmethyl)x-oxycarbamoyl-heparin" (or broadly "silyl-heparin") is disclosed as the specific embodiment(s), it is considered that the meaning of the claims should be clear from the wording of the claim alone.

Applicant could overcome this rejection by amending "a conjugate of at least one prosthetic hydrophobic unit and a heparin activity biomolecule" to "silyl-heparin".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-2, 4-12, 16 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Hossainy et al. (USP 6585765).

Hossainy teaches a method of impregnating an implantable device, such as a vascular graft or a covering adapted to be disposed over a prosthesis comprising applying said device with a solution comprising a pre-polymer crosslinking agent (e.g., polyethylene glycol, polyvinylpyrrolidone, dimethylaminoethyl methacylate, etc...) dissolved in first fluid (e.g., acetone, isopropanol and ethanol) and applying said device with a solution comprising a cross-linkable therapeutic agent (e.g., antineoplasti, anti-inflammatory, antiplatelet, anticoagulant, antifebrin, antithrombin, antimiotic, etc..., particularly heparin) dissolved in second fluid (e.g., water, acetone, isopropanol, ethanol and freon, particularly deionized water) wherein said crosslinking agent is crosslinked with said therapeutic agent, forming hydrogel and impregnated to said device; wherein the another fluid or a plurality of other fluids (mixed with the first and/or second fluid contained in the composition) is applied to implantable device (abstract; claims 1-4, 6-7, 10-13, 17-52; column 13, line 66 through column 14, line 51; column 12, lines 17-31; column 11, lines 32-33 and 53-62; column 5, line 60 through column 6, line 40; column

9, line 66 through column 10, line 7; column 11, lines 13-26); and wherein said body of device is composed of open-pored material such as expanded polytetrafluoroethylene, polyethylene terephthalate and plyurethane (column 1, lines 32-45; column 4, lines 28-34; Examples; claim 3). Hossainy also teaches that the concentration of polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), pluronic or polyacrylamide in the composition should be about 15-30% by weight of the total weight of the composition (column 11, lines 44-49).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 3, 14-15, 17 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hossainy et al. (USP 6585765).

The teaching of Hossainy has been discussed in above 102(e) rejection.

The teaching of Hossainy differs from the claimed invention in (i) the specific amounts of water in the second solution, (ii) the specific amount of the bis-variant of polyethylene glycol, polyethylene oxide or polyethylene glycol, and (iii) the specific immersing time.

With respect to the specific amount of water in second solution, namely "about 10 to 80 percent water by volumne", or the specific amount of polyethylene glycol, namely "between about 0.001 mg/ml and 500 mg/ml" or "at a concentration between about 02 mg/ml and 10 mg/ml", such determination of the appropriate amounts of known active and/or inactive ingredients in process of impregnating or coating medical device which involves each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed herein. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to determination of immersing time, specifically "between about 5 minutes and two hours", "between about 15 minutes and about one hour", "between

about 45 minutes and about 75 minutes" in claims 26-28, the cited reference does not specifically mention about the required immersing time. Generally difference in time will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such time is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable time by routine experimentation.

7. Claims 13 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hossainy et al. (USP 6585765) in view of Sawney (USP 6818018) in view of Tsang et al. (USP 5955588).

The teaching of Hossainy has been discussed in above 102(e) rejection.

The teaching of Hossainy differs from the claimed invention in the use of bis-(benzotriazole carbonate) polyethylene glycol and benzyl-bis(dimethylsilylmethyl)x-oxycarbamoyl-heparin in said composition.

Sawney teaches an advantage of using PEG derivatives including bis-(benzotriazole carbonate) polyethylene glycol as crosslinking agent in forming hydrogel coating material for medical device (abstract; column 10, lines 8-11; column 14, line 36; column 20, lines 26-29; Examples 1 and 8).

Tsang teaches an advantage of using benzyl-bis(dimethylsilylmethyl)x-oxycarbamoyl-heparin (in suitable solvents such as methanol, ethanol, propanol, etc...) as an anti-thrombogenic coating material for a medical device (abstract; column 2, lines 33-41 and lines 64-67; column 3, lines 5-26; column 7, lines 3-57; column 7 line 66 through column 9, line 12). Tsang also teaches

One having ordinary skill in the art would have been motivated to the teaching of Hossainy and combine the references to prepare medical device with better anti-thrombogenic effects over time and improved or enhanced pharmacological properties of medial and surgical applications. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the specific amount of the cross-linkable adsorbable biomolecule such as benzyl-bis(dimethylsilylmethyl)x-oxycarbamoyl-heparin, namely "from about 0.01% to about 10%" or "from about 0.25% to about 1.5%", such determination of the appropriate amounts of known active and/or inactive ingredients in process of impregnating or coating medical device which involves each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed herein.

Conclusion

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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